Diagnostic Performance of TE, 2D-SWE And MRE For Liver Fibrosis In Treatment-Naive People With HBV: A Systematic Review And Meta-Analysis

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Research Article

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Abstract

Background/aims: To assess the performance of transient elastography (TE), two-dimensional shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE) for staging significant fibrosis and cirrhosis in untreated chronic hepatitis B (CHB) patients.

Methods: Pubmed, Embase, Web of Science and Cochrane Library were searched for terms involving CHB, TE, SWE, and MRE. Other etiologies of chronic liver disease (CLD), previous treatment in patients or articles not published in SCI journals were excluded. Hierarchical non-linear models were used to evaluate the diagnostic accuracy of TE, 2D-SWE and MRE. Heterogeneity was explored via analysis of threshold effect and meta-regression.

Results: Twenty-eight articles with a total of 4540 untreated CHB patients were included. The summary AUROC using TE, 2D-SWE and MRE for predicting significant fibrosis (SF) were 0.84, 0.89, and 0.99, respectively. MRE is more accurate than both TE ($P=0.01$) and 2D-SWE ($P=0.01$) in staging SF. 2D-SWE is superior to TE in detecting SF ($P=0.01$). The summary AUROC employing TE, 2D-SWE and MRE for detecting cirrhosis were 0.9, 0.94, and 0.99, respectively. TE displayed a similar diagnostic accuracy with 2D-SWE in staging cirrhosis ($P=0.14$). MRE and 2D-SWE are comparable for staging cirrhosis ($P=0.08$). MRE is superior than TE ($P=0.01$) in staging cirrhosis.

Conclusion: TE, 2D-SWE, and MRE express acceptable diagnostic accuracies in staging significant fibrosis and cirrhosis in untreated CHB patients. Both MRE and 2D-SWE are better choices while the TE can be regarded as a secondary option.

Introduction

Despite the availability of effective drug interventions that reduce or prevent complications in most cases, chronic hepatitis B (CHB) remains a major public health issue worldwide that poses a significant health burden [1]. As the causative agent of CHB, human hepatitis B virus (HBV) is a hepatotropic DNA virus that can trigger acute and chronic hepatitis, contributing to HBV-related cirrhosis and even hepatocellular carcinoma [2]. Due to the lack of early signs in patients with HBV-related compensated cirrhosis, liver biopsy in the asymptomatic population is inadequate, and early diagnosis of HBV-related cirrhosis is not easy [3]. In the majority of cases, at the time of inpatient visits, the disease tends to progress to a decompensated period. Patients tend to suffer from various serious or even fatal complications, namely esophageal-gastric varices bleeding, refractory ascites, and hepatocellular carcinoma [4]. Several avenues point out that the progression of liver fibrosis can be halted or even reversed by early diagnosis, dynamic assessment and effective intervention that blocks persistent damage to the liver [5]. Hence, early detection of fibrosis and effective intervention of the related etiology are extremely fundamental to improve the prognosis of patients with chronic liver disease (CLD) [6].

Liver biopsy is the gold standard for assessing hepatitis and fibrosis. However, invasiveness, sampling error and inter-observer variations limit its clinical application [7]. More researchers have focused on noninvasive methods to more accurately assess liver fibrosis.

Imaging techniques such as transient elastography (TE), shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE) have been proven to efficiently and precisely assess fibrosis efficiently and precisely in CHB patients. TE, also known as FibroScan, has been recommended by the World Health Organization for assessing fibrosis and has become widely present in clinical practice [8]. 2D-SWE is a well-validated device ultrasonographic elastography technique with various strengths such as offering a more precise region of interest (ROI) and monitoring blood flow alterations for high-quality measurements. Growing evidence has revealed that 2D-SWE is a favorable choice for staging fibrosis in CHB patients [9]. MRE is another elastography technique that utilizes a modified phase-contrast imaging sequence to estimate fibrosis via shear waves within the whole liver. Thus far, MRE has been considered the most accurate noninvasive method to assess liver fibrosis in CLD with great reliability and reproducibility [10].

These three imaging techniques have been proven to exhibit promising results for quantification of liver fibrosis with considerable accuracies. Dong et al [11] concluded that MRE and 2D-SWE are excellent tools for staging fibrosis in patients with CHB. Nevertheless, they also included studies regardless of whether the patients were receiving antiviral therapy or not. Indeed, there is an urgent need to stage fibrosis for treatment-naïve people with HBV. Given that CHB is a dynamic disease, persons who are not receiving treatment need be assessed regularly to determine whether to initiate antiviral treatment (AVT). If the biopsy specimen shows significant fibrosis (SF) in patients with elevated HBV DNA levels, AVT is recommended based on the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance [12].

The AASLD suggests that adults with compensated cirrhosis and low-level viremia ($< 2,000$ IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level [12]. To better tune the timing of AVT, we conduct a meta-analysis to compare the diagnostic performance of TE, 2D-SWE, and MRE for staging SF and cirrhosis in treatment-naïve people with HBV.

Materials And Methods

This study was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13]. The protocol was registered with PROSPERO (CRD42021248023).

Articles search strategy

The specific search strategy is listed in Supplementary Table 1. Four authorized online databases, namely Pubmed, Embase, the Web of Science, and the Cochrane Library (01/01/2000-01/02/2021) were screened utilizing the following words: hepatitis b, liver fibrosis, FibroScan, transient elastography, shear wave elastography and magnetic resonance elastography.

Eligibility criteria

The following situations were considered as the inclusion criteria: 1) the accuracies of 2D-SWE, TE or MRE for discriminating liver fibrosis in CHB patients were investigated; 2) the specific liver fibrosis stage of each patient was biopsy-proven; 3) the sensitivity, specificity and the number of patients in each fibrosis stage could be extracted to create 2×2 table of test performance; 4) at least 50 patients were enrolled in each investigation; and 5) the original articles need to be published in English and could be screened in SCI journals. The following situations were considered as the exclusion criteria: 1) the original articles did not focus on the diagnostic performance of TE, 2D-SWE or MRE; 2) special types of work such as patent, book section, case report, reply, letter, commentary, conference abstracts, review or meta-analysis were excluded; 3) studies on children or animal; 4) insufficient data to create 2×2 table of test performance; 5) patients were co-infected with other viral hepatitis or HIV; 6) patients were diagnosed as CLD triggered by other etiologies such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) and autoimmune liver disease; 7) patients had already received antiviral therapy, hepatectomy or liver transplant before biopsy or imaging tests; 8) patients were identified as hepatic carcinoma before TE, 2D-SWE, MRE, or liver biopsy; 9) unclear interval between imaging tests and liver biopsy or unclear liver biopsy size.

Identification of liver fibrosis

Significant fibrosis (SF) and cirrhosis were identified as stages F2-F4 and F4 using the corresponding scoring systems such as Scheuer, Ishak, Metavir, Batts-Ludwig, and Knodell.

Data acquirement

Two experienced researchers (ML and SW) were first invited to screen the online databases and make preliminary selections. The eligibility and quality of each article were screened by each investigator. Two researchers then extracted the targeted data separately. Basic characteristics, technical characteristics of the included studies as well as the diagnostic performance of these three noninvasive approaches were summarized in our predesigned forms.

Quality assessment

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was employed to conduct the evaluation of the quality of the included studies. The results of the QUADAS evaluation were visualized through Review Manager 5.3 (The Cochrane Collaboration). A third investigator (XW) was then invited to assess the discrepancies between the two researchers. The variation between the investigators were resolved through a discussion.

Data synthesis and statistical analysis

The demographic characteristic of the included patients were presented as mean±standard deviation (SD) or median±interquartile range. The number of true positives (tp), false positives (fp), false negatives (fn), and true negatives (tn) was calculated based on the reported population in each biopsy-proven fibrosis stage, sensitivity, and specificity of these three noninvasive imaging methods. Once the 2×2 table comprised of tp, fp, fn and tn was completed, the summary positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUROC), positive likelihood ratio (LR) and negative LR were calculated according to the corresponding formulas. For meta-analysis, the pooled sensitivity and specificity were presented with midas and metanif modules in Stata 16.0 (StataCorp LP) [14]. The summary diagnostic odds ratios (DORs) were calculated utilizing a Der-Simonian and Laird random effects model with a corresponding test of heterogeneity. Hierarchical non-linear models including HSROC model and the bivariate model were used in our study to evaluate the diagnostic accuracy. The non-threshold heterogeneity was presented with the Q - I^2 statistic in the forest plots. An I -squared value >50% was regarded as a threshold for determining substantial statistical heterogeneity [15]. SAS 9.4 (SAS Institute Inc) with a “mixed” command was utilized for the multiple comparisons of the sensitivity and the specificity among TE, 2D-SWE and MRE [16]. R 4.0.3 (R Foundation for Statistical Computing) with “mada” was utilized to compare the fitted SROC curves of TE, 2D-SWE, and MRE [17]. The pairwise comparisons of the AUROC values were conducted through the DeLong test [18]. A P value < 0.05 was considered to indicate statistically significant differences.

Publication bias

Deeks’ funnel plots were generated by Stata 16.0 with “midas” command and a “mylabels” package for the evaluation of publication bias of the included studies. A P < 0.05 was considered to indicate the existence of publication bias.

Exploration of heterogeneity

As different cut-off values were adopted in individual studies, the threshold effect was evaluated via spearman correlation analysis of the sensitivity and the specificity with MetaDisc 1.4. Meta-regression analysis were used to evaluate the influence of seven characteristics of individual studies on AUROC, namely the location of the study population (Asia vs Europe), study design (prospective cohort study vs retrospective cohort study or cross-sectional study), mean biopsy length (<20 mm vs ≥20 mm), mean ALT (<5 ULN vs ≥5 ULN), liver biopsies scoring system (Metavir vs non-Metavir), the interval between biopsy and imaging test (<3 months vs ≥3 months), study quality (all question score yes vs one or more questions scored no or unclear).

Results

Characteristics and the Quality of the Retrieved Studies

The flow diagram of the study selection is presented in Figure 1. 4190 records were retrieved utilizing our primary search strategies. 3609 articles were identified after duplications removed. After excluding the studies that did not fulfill the eligibility criteria, 28 studies were ultimately included, which were listed in the reference portion of Supporting Information. Table 1-2 offer the basic characteristics and the technical characteristics of the included studies. 4540 subjects (mean age, 42.3 years; 67.2% male) were included. Because of the high hepatitis B prevalence in China, the majority of the included studies were from

Asia (90%). In addition to 7 (25%) retrospective studies, 21 (75%) studies were based on prospective design. Regarding the QUADAS-2 score, 5 (17.9%) studies scored 14 points. 16 (57.1%), 6 (21.4%) and 1 (3.5%) study scored 13, 12, 11, and 10 points, respectively.

Table 1 Basic characteristics of the Included Studies

Study id	Region	Imaging	Design	Center	Subject	Study time	Mean age (y)	Male (%)	BMI (kg/m2)	ALT (U/L)	ALT≥5ULN excluded	HBeAg (+) (%)	HBV (log IU/r
Cardoso 2011	France	TE	Cross sectional	Single center	202	2006-2008	49	60	24.4 ± 3.5*	92 (40-112)†	Yes	24	4.9%
Gaia 2011	Italy	TE	Prospective	Single center	70	2007-2009	44	71.4	24.3 (16.7-33.1)§	70 (13-464)§	No	NA	Det
Hennedige 2017	Singapore	MRE	Retrospective	Single center	63	2009-2012	50.1	69.8	24.9 ± 4*	NA	No	NA	NA
Jekarl 2018	Korea	TE	Retrospective	Single center	151	2011-2013	44.6	66.9	NA	2.08 ± 2.67*	Yes	NA	6.4
Leung 2013	China	TE, SWE	Prospective	Single center	226	2011-2012	48.8	65	24.2 (21.6-27.3)†	69 (37.5-105)†	No	100	5.6
Li 2018	China	TE	Retrospective	Single center	118	2013-2015	37	62.8	22.5 (20.4-24.2)†	39 ± 16*	Yes	66	5.4 (7.5)
Liu 2019	China	SWE	Prospective	Single center	123	2016-2018	36.3	49.6	20.5 ± 2.2*	33.5 ± 22.3*	Yes	60.2	6.6 (8.0)
Liu 2014	China	TE	Prospective	Single center	108	2011-2012	40.1	75	22 ± 3*	53.2 (8-270)§	No	NA	NA
Park 2019	South Korea	SWE, MRE	Retrospective	Single center	63	2013-2018	50.8	58.7	23.4 ± 3.4*	44 ± 20.8*	Yes	55.6	5.7 (±1.6)
Seo 2015	South Korea	TE	Retrospective	15 Centers	567	2006-2014	45	66.7	23.8 (22.1-25.7)†	48 (35-56)†	Yes	NA	NA
Shi 2014	China	MRE	Prospective	Single center	113	2012-2013	42	42.5	21.71 (17.8-32.6)§	NA	No	NA	Det
Trembling 2014	Italy	TE	Prospective	Single center	182	NA	46	71	NA	110.3 ± 103.4*	No	29.1	NA
Venkatesh 2014	Singapore	MRE	Prospective	Single center	63	2009-2011	50	69.8	24.82 ± 3.97*	71.75 ± 101.8*	No	NA	NA
Yao 2020	China	TE, SWE	Retrospective	Single center	54	2013-2015	36.7	76	23.9 (21.9-25)†	50.4 (28.8-129.2)†	No	61	4.8 (6.3)
Zeng 2017	China	TE, SWE	Prospective	Single center	257	2013-2015	36.7	77.4	21.7 (19.7-23.9)†	42 (28.3-67.8)†	No	NA	NA
Zeng 2014	China	SWE	Prospective	Single center	104	2011-2012	37.2	78.8	22.1 ± 3.4*	43 (28-74)†	No	NA	Det
Zhang 2015	China	TE	Retrospective	Single center	180	2011-2013	36.43	77.2	24.36 ± 3.52*	93.88 ± 116.82*	No	NA	4.6 (2.6)
Osakabe 2011	Japan	TE	Prospective	Single center	51	2005-2009	51	36.8	NA	34 (20.3-80)†	No	32.5	4.6
Cho 2011	Korea	TE	Prospective	Single center	121	2006-2009	39.1	66.9	23.9 ± 3.0*	167.0 ± 197.9*	No	NA	Det
Kim BK 2012	Korea	TE	Prospective	Single center	194	2008-2010	46.7	61.3	23.4 ± 2.8*	58.4 ± 27.1*	No	NA	NA
Kim US 2012	Korea	TE	Prospective	Single center	150	2007-2009	41.9	71.3	23.2 ± 2.8*	74.1 ± 98.3*	No	NA	NA
Kumar 2013	India	TE	Prospective	Single center	200	2009-2011	37.6	79.5	24.2 ± 3.7*	44 (9-320)§	No	40.5	5.6 (3.3-8.8)
Zhao 2017	China	TE	Prospective	Single center	99	2014-2015	37.7	64.6	23.87 ± 3.42*	46.73 ± 30.19*	Yes	NA	NA
Shen 2019	China	TE	Prospective	Single center	593	2014-2015	37	63.7	NA	NA	Yes	59.5	NA

Kim Do 2009	Korea	TE	Prospective	Single center	91	2005-2006	42.5	79.2	25.3 ± 1.3*	45.1 ± 23.4*	No	58.5	NA
Kim US 2009	Korea	TE	Prospective	Single center	130	2006-2007	40	80.2	23.8 ± 4.6*	46 ± 24*	No	59.3	50.1 deta
Chan 2009	China	TE	Prospective	Single center	161	2006-2008	45	76	24 ± 4*	93 ± 78*	No	43	6.5
Wu 2015	China	MRE	Prospective	Single center	106	2011-2013	59	48.7	NA	NA	No	NA	NA

*Mean±SD.

†Median (interquartile range).

§Median (range).

AVT, antiviral treatment; BMI, body mass index; MRE, magnetic resonance elastography; NA, not available; QUADAS, Quality Assessment of Studies of Diagnostic Accuracy Studies; SWE, shear wave elastography; TE, Transient Elastography; ULN, upper limit of normal.

Table 2 Technical characteristics of imaging and histological examination

Id	Author	year	Imaging	Instrument detail	Scoring system	Interval	Length
1	Cardoso	2011	TE	M probe (1-6 MHz)	Metavir	1 day	≥15 mm
2	Gaia	2011	TE	M probe (1-6 MHz)	MEtavir	6 months	≥20 mm
3	Hennedige	2017	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	6 months	≥15 mm
4	Jekarl	2018	TE	M probe (1-6 MHz)	Knodell	1 day	≥20 mm
5	Leung	2013	TE, SWE	M probe (1-6 MHz); SC6-1 probe (1-6 MHz)	Metavir	1 year	≥15 mm
6	Li	2018	TE	M probe (1-6 MHz)	Metavir	6 months	≥15 mm
7	Liu	2014	TE	M probe (1-6 MHz)	Metavir	1 day	15–19 mm
8	Liu	2019	SWE	SC6-1 probe (1-6 MHz)	Scheuer	1 day	≥15 mm
9	Park	2019	SWE, MRE	SC6-1 probe (1-6 MHz); 3T (unclear frequency), unclear sequence	Metavir	2weeks	≥10mm
10	Seo	2015	TE	M probe (1-6 MHz)	Batts and Ludwig	3 months	15-30 mm
11	Shi	2014	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	23 days	14±7 mm
12	Trembling	2014	TE	M probe (1-6 MHz)	Metavir	1 day	≥20 mm
13	Venkatesh	2014	MRE	1.5T (60 Hz); 2D-GRE sequence	Metavir	6 months	≥18 mm
14	Yao	2020	TE, SWE	M probe (1-6 MHz); SC6–1 probe (1-6 MHz)	Ishak	1 month	≥20 mm
15	Zeng	2014	SWE	SC6-1 probe (1-6 MHz)	Metavir	3 days	≥15 mm
16	Zeng	2017	TE, SWE	M probe (1-6 MHz); SC6–1 probe (1-6 MHz)	Metavir	3 days	≥15 mm
17	Zhang	2015	TE	M probe (1-6 MHz)	Scheuer	3 days	≥15 mm
18	Osakabe	2011	TE	M probe(1-6MHz)	Metavir	<1month	≥15mm
19	Cho	2011	TE	M probe(1-6MHz)	Metavir	<1day	≥15mm
20	Kim BK	2012	TE	M probe(1-6MHz)	Batts and Ludwig scoring system	<1day	≥20mm
21	Kim US	2012	TE	M probe(1-6MHz)	Laennec	<1day	≥15mm
22	Kumar	2013	TE	M probe(1-6MHz)	Metavir	<1week	≥15mm
23	Zhao	2017	TE	M probe(1-6MHz)	Metavir	<1day	≥15mm
24	Shen	2019	TE	M probe(1-6MHz)	Metavir	<1week	≥15mm
25	Kim Do	2009	TE	M probe(1-6MHz)	Metavir	<1day	≥10mm
26	Kim US	2009	TE	M probe(1-6MHz)	Metavir	<1day	≥15mm
27	Chan	2009	TE	M probe(1-6MHz)	Metavir	<1month	≥15mm
28	Wu	2015	MRE	1.5T(60Hz);2D-GRE sequence	Metavir	3months	≥10mm

MRE, magnetic resonance elastography; SWE, shear wave elastography; TE, Transient Elastography.

Diagnosing SF

Twenty-three studies (3879 untreated patients) focused on the diagnostic performance of TE, 2D-SWE, and MRE for staging SF. Specifically, 16 (3244 patients), 6 (827 patients), and 5 (408 patients) studies investigated the TE, 2D-SWE, and MRE.

Table 3 demonstrates the diagnostic performance of these three methods for staging SF. The pooled sensitivity and specificity of TE were 0.76 (95% CI, 0.72–0.79) and 0.79 (95% CI, 0.75–0.83), respectively. As shown in Figure 2, the summary AUROC of TE was 0.84 (95% CI, 0.81–0.87). Regarding the 2D-SWE, the pooled sensitivity and specificity were 0.84 (95% CI, 0.8–0.88) and 0.84 (95% CI, 0.76–0.89). The AUROC was 0.89 (95% CI, 0.86–0.92). The overall diagnostic performance of MRE is 95% sensitivity, 96% specificity and 99% accuracy, at cut-off values ranged from 2.47 to 4.07 kpa.

Table 3 Summary sensitivity, specificity, PLR, NLR, DOR and AUROC of TE, SWE and MRE for staging fibrosis by bivariate analysis

Imaging test	No. of studies (No. of patients)	Cut-off Values	Sensitivity(95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUROC (95% CI)
Staging SF							
TE	16 (3244)	6-8.8	0.76 (0.72-0.79)	0.79 (0.75-0.83)	3.65 (3.08-4.32)	0.31 (0.26-0.36)	0.84 (0.81-0.87)
SWE	6 (827)	6.73-9.05	0.84 (0.8-0.88)	0.84 (0.76-0.89)	5.15 (3.47-7.66)	0.19 (0.15-0.24)	0.89 (0.86-0.92)
MRE	5 (408)	2.47-4.07	0.95 (0.88-0.98)	0.96 (0.91-0.98)	24.94 (10.14-61.3)	0.06 (0.02-0.13)	0.99 (0.97-0.99)
Staging Cirrhosis							
TE	19 (3806)	8-14.1	0.84 (0.78-0.88)	0.84 (0.8-0.88)	5.1 (4.13-6.3)	0.19 (0.14-0.26)	0.9 (0.88-0.93)
SWE	5 (773)	9.5-11.8	0.91 (0.82-0.96)	0.89 (0.84-0.92)	7.97 (5.61-11.32)	0.1 (0.04-0.21)	0.94 (0.92-0.96)
MRE	5 (408)	3.46-6.87	0.96 (0.85-0.99)	0.96 (0.92-0.98)	25.68 (11.28-58.47)	0.04 (0.01-0.16)	0.99 (0.98-1)

AUROC, area under summary receiver operating characteristic; CI, confidence interval; DOR, diagnostic odds ratio; MRE, magnetic resonance elastography; PLR, positive likelihood ratio; NLR, negative likelihood ratio; SF, significant fibrosis; SWE, shear wave elastography; TE, transient elastography.

Pairwise comparisons was shown in Table 4. MRE expressed higher sensitivity than both TE ($F=18.89$, $P<0.01$) and 2D-SWE ($F=6.13$, $P<0.01$). MRE exhibited greater specificity than both TE ($F=13.67$, $P<0.01$) and 2D-SWE ($F=8.83$, $P<0.01$). Compared with TE, 2D-SWE displayed greater sensitivity ($F=5.57$, $P=0.02$). The specificity of TE and 2D-SWE were comparable ($F=0.92$, $P=0.34$). As presented in Supplementary Figure 2 and Table 4, MRE was more accurate than both TE ($Z=8.88$, $P<0.01$) and 2D-SWE ($Z=5.16$, $P<0.01$). 2D-SWE was superior to TE ($Z=3.53$, $P<0.01$). As shown in Figure 3, in descending order, the combined DORs of MRE, 2D-SWE, and TE for staging SF were 299.18 ($I^2=0$, $P=0.565$), 26.3 ($I^2=30.5\%$, $P=0.207$), 11.59 ($I^2=49.5\%$, $P=0.013$).

Table 4 Pairwise comparison of the pooled sensitivity, specificity and AUROC values of TE, SWE, and MRE for staging fibrosis

Staging fibrosis	Pairwise comparisons	Sensitivity		Specificity		AUROC	
		F value	P value	F value	P value	Z value	P value
Staging SF	TE vs. SWE	5.57	0.02	0.92	0.34	3.53	<0.01
	SWE vs. MRE	6.13	0.01	8.83	<0.01	5.16	<0.01
	TE vs. MRE	18.89	<0.01	13.67	<0.01	8.88	<0.01
Staging cirrhosis	TE vs. SWE	2.35	0.13	3.04	0.08	1.47	0.14
	SWE vs. MRE	0.37	0.55	3.92	0.04	1.73	0.08
	TE vs. MRE	4.06	0.04	12.4	<0.01	4.71	<0.01

AUROC, area under summary receiver operating characteristic; MRE, magnetic resonance elastography; SF, significant fibrosis; SWE, shear wave elastography; TE, transient elastography.

Diagnosing Cirrhosis

Twenty-six studies (with 4441 treatment-naïve CHB patients) investigated these three noninvasive methods for the prediction of cirrhosis. 19 (3806 patients), 5 (773 patients), and 5 (408 patients) items focused on the TE, 2D-SWE, and MRE, respectively for diagnosing cirrhosis.

Table 3 summarizes the diagnostic performance of these three methods for staging cirrhosis. The pooled sensitivity and specificity of TE were 0.84 (95% CI, 0.78-0.88) and 0.84 (95% CI, 0.8-0.88). As shown in Figure 2, the summary AUROC of TE was 0.9 (95% CI, 0.88-0.93). Regarding the 2D-SWE, the pooled sensitivity and specificity were 0.91 (95% CI, 0.82-0.96) and 0.89 (95% CI, 0.84-0.92). The AUROC of 2D-SWE was 0.94 (95% CI, 0.92-0.96). The overall diagnostic performance of MRE is 96% sensitivity, 96% specificity and 99% accuracy, at cut-off values ranged from 3.46 to 6.87 kpa.

Pairwise comparisons were shown in Table 4. MRE expressed higher sensitivity than MRE ($F=4.06$, $P=0.04$). MRE expressed similar sensitivity with 2D-SWE ($F=0.37$, $P=0.55$). MRE expressed higher specificity than both TE ($F=12.4$, $P<0.01$) and 2D-SWE ($F=3.92$, $P=0.04$). Compared with TE, 2D-SWE displayed similar sensitivity with TE ($F=2.53$, $P=0.13$). The specificity of 2D-SWE was comparable to that of TE ($F=3.04$, $P=0.08$). As presented in Supplementary Figure 2 and Table 4, MRE was more accurate than TE ($Z=4.71$, $P<0.01$). MRE displayed similar accuracy with SWE ($Z=1.73$, $P=0.08$). The accuracies of 2D-SWE and TE were comparable ($F=1.47$, $P=0.14$). As shown in Figure 4, in descending order, the combined DORs of MRE, 2D-SWE, and TE for staging cirrhosis were 223.9 ($I^2=0$, $P=0.607$), 70.62 ($I^2=59.6\%$, $P=0.042$) and 24.21 ($I^2=58.7\%$, $P=0.001$).

Heterogeneity and Publication Bias

Non-threshold heterogeneity was observed in TE, 2D-SWE and MRE for detecting significant fibrosis and cirrhosis (Supplementary Table 3). A meta-regression analysis can only be conducted in groups of more than 10 studies with complete data to examine the methodological heterogeneity. In groups larger than 10 studies, heterogeneity existed when TE was used for staging fibrosis. The diagnostic accuracy was not affected by the following factors when TE was used for staging significant fibrosis and cirrhosis: study design ($P = 0.18$ and 0.87), classification criteria ($P = 0.5$ and 0.21), region ($P = 0.4$ and 0.49), interval between biopsy and imaging test ($P = 0.55$ and 0.32), obviously abnormal ALT ($P = 0.9$ and 0.94), liver biopsy length ($P = 0.33$ and 0.71), and QUADAS-2 score ($P = 0.1$ and 0.94). There was no evidence of publication bias for TE, 2D-SWE and MRE for staging fibrosis (Supplementary Figure 3).

Discussion

In this meta-analysis, we evaluated the diagnostic performance of TE, 2D-SWE and MRE for staging fibrosis in CHB. This study demonstrates that TE, 2D-SWE, and MRE express acceptable diagnostic accuracies to stage significant fibrosis and cirrhosis in treatment-naïve people with HBV. Additionally, for staging SF and cirrhosis, both MRE and 2D-SWE are both the best choices while TE can be regarded as a secondary option. For staging SF, the summary AUROC value of MRE is significantly greater than that of 2D-SWE (0.99 vs 0.89 , $P < 0.01$) and TE (0.99 vs 0.84 , $P < 0.01$). 2D-SWE is superior to TE (AUROC = 0.89 vs 0.84 , $P < 0.01$). For discriminating cirrhosis, MRE is superior to TE (AUROC = 0.99 vs 0.9 , $P < 0.01$), but comparable to 2D-SWE (AUROC = 0.99 vs 0.9 , $P = 0.08$). Moreover, the diagnostic accuracy of MRE for staging SF and cirrhosis was both greater than 0.95 using AUROC, at cut-off values 2.47 – 4.07 kpa and 3.46 – 6.87 kpa. MRE expressed the best diagnostic performance for staging SF and cirrhosis, which is also consistent with previous findings in patients with CLD [19; 20]. For discriminating cirrhosis in patients with other etiologies such as NAFLD, MRE and 2D-SWE were also comparable. Both MRE and 2D-SWE were regarded as better choices for staging cirrhosis [21].

Venkatesh et al. [22] confirmed that normal LSM assessed through MRE in normal Asian population is highly reproducible. The results were not affected by age, sex and body mass index (BMI). MRE can visualize the whole substantive organ without an accurate acoustic window, which is superior to TE [23]. A larger measurement area of the liver can effectively lower the sampling errors [24]. Ichikawa et al. [25] explained that TE can only conduct a unidirectional measurement, which is more likely to be interfered with reflection wave and refraction wave. In terms of MRE, it evaluates the two-dimensional (2D) or even three-dimensional (3D) displacement vector. Additionally, compared with TE, MRE can generate better quality of figures with compressional and continuous waves. Because MRE conducted with gradient-recalled echo (GRE) sequence has been well-validated in previous large cohorts of clinical studies [26], the most commonly applied commercial MRE technique is GRE-MRE [27]. Nevertheless, the conventional GRE-MRE technique tend to be technically deficient as the process of its imaging is easily susceptible to the iron deposition. Hence, GRE-MRE is rather time-consuming and a more stringent breath hold by the patients is required [28]. To lower these barriers, spin-echo-based echo planar imaging (SE-EPI) MRE sequence was developed. This novel sequence is less sensitive to the iron-overload and thus contributing to shorter imaging time and a higher technical success rate [29]. Despite the promising advances, MRE is currently time-consuming and costly. Considering the high prevalence of CHB and the scarcity of MRE in Asian countries, there is still a long way to popularize MRE for CHB patients on a large scale.

Compared with TE, easier access to the ROI with high quality measurements with a colorful elasticity map would be accessible through 2D-SWE [30]. Moreover, the variation of blood flow can be monitored through 2D-SWE [31; 32]. As inspired by its advantages and indicated by the results in our article, 2D-SWE may be a better choice to stage SF than TE.

There are still limitations in this study. First, due to the incomplete data, our meta-regression analysis did not include the factors such as obesity, ascites, HBV-DNA, which may also be the sources of heterogeneity and thus affecting our ultimate conclusions [33]. Surprisingly, Petzold et al. [34] pointed out that parameters such as age, gender, BMI, and liver function indexes had no significant impact on LSM measured by 2D-SWE. It is worth noting that the LSM measured through TE tends to be affected by inflammation, congestion, and cholestasis [35] and thus affecting our judgments. Second, this study did not take the financial cost, the convenience or success rate of examination into consideration. A cheaper and less time-consuming technique would lower the barrier for clinical applications [36]. Moreover, regarding 2D-SWE and MRE, although AUROCs are high, the number of studies on which rely these findings is rather small ($n = 6$ and 827 patients; $n = 5$ and 408 patients), limiting the persuasiveness of our conclusions. Therefore, more prospective and multicenter studies are needed.

Collectively, our current study confirms that TE, 2D-SWE, and MRE express acceptable diagnostic accuracies in staging fibrosis in treatment-naïve people with HBV. MRE and 2D-SWE are both the best choices while TE can be regarded as a secondary option to stage SF and cirrhosis in untreated CHB patients.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; AUROC, area under the receiver operating characteristic curve; AVT, antiviral treatment; CHB, chronic hepatitis B; DOR, diagnostic odds ratio; HBV, hepatitis B virus; LR, likelihood ratio; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; QUADAS, quality assessment of diagnostic accuracy studies; ROC, receiver operating characteristic; SF, significant fibrosis; sROC: summary receiver operating characteristic; 2D-SWE, two-dimensional shear wave elastography; TE, transient elastography.

Declarations

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Author contributions MKL, XYW and BW contributed to the literature search and data extraction. MKL and XYW conducted the study quality assessment. MKL and XYW performed the study design and data analysis. MKL drafted the manuscript. XYW and BW made the critical revision of the paper. BW contributed to

the study conception and study supervision.

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Compliance with ethical standards

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

Clinical trials registration Not applicable.

Data sharing We agree with the policy in the journal.

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Figures

Figure 1

Flow diagram of the study selection. 150×200mm (300×300 DPI)

Staging significant fibrosis:

Staging cirrhosis:

Figure 2

The HSROC plots of TE, 2D-SWE and MRE for the sensitivity and specificity in fibrosis stage $F \geq 2$ and $F = 4$. The study estimate represents the data of each included study and the size of the circle represents the weight of each study based on the number of patients; the summary point represents the summary sensitivity and specificity; the 95% confidence region represents the 95% confidence interval of the summary sensitivity and specificity; the 95% prediction region represents 95% confidence interval of sensitivity and specificity of each individual study included in the meta-analysis. (A) HSROC plot of TE for fibrosis stage $F \geq 2$, (B) HSROC plot of 2D-SWE for fibrosis stage $F \geq 2$, (C) HSROC plot of MRE for fibrosis stage $F \geq 2$, (D) HSROC plot of TE for fibrosis stage $F = 4$. (E) HSROC plot of 2D-SWE for fibrosis stage $F = 4$. (F) HSROC plot of MRE for fibrosis stage $F = 4$. 150×150mm (300×300 DPI)

Figure 3

Forest plot of tests. (A) TE in detecting significant fibrosis. (B) 2D-SWE in detecting significant fibrosis. (C) MRE in detecting significant fibrosis. 150×300mm (300×300 DPI)

Figure 4

Forest plot of tests. (A) TE in detecting cirrhosis. (B) 2D-SWE in detecting cirrhosis. (C) MRE in detecting cirrhosis. 150×300mm (300×300 DPI)

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